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The Comptroller
The Patent Office

1987
19167

REQUEST FOR GRANT OF A PATENT

8719167

THE GRANT OF A PATENT IS REQUESTED BY THE UNDERSIGNED ON THE BASIS OF THE PRESENT APPLICATION

I Applicant's or Agent's Reference *(Please insert if available)* SG303

II Title of Invention CHEMICAL COMPOUNDS

III Applicant or Applicants *(See note 2)*

Name (First or only applicant) Glaxo Group Limited

Country United Kingdom State ADP Code No.

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Name (of second applicant, if more than one)

Country State

Address

IV Inventor (see note 3)

(a) The applicant(s) is/are the sole/joint inventor(s)
or
(b) A statement on Patents Form No 7/77 is/will be furnished

V Name of Agent (if any) *(See note 4)* ELKINGTON AND FIFE ADP CODE NO

VI Address for Service (See note 5) High Holborn House
52/54 High Holborn
London WC1V 6SH

VII Declaration of Priority (See note 6)

Country	Filing date	File number
-	-	

VIII The Application claims an earlier date under Section 8(3), 12(6), 15(4), or 37(4) (See note 7)

Earlier application or patent number and filing date

IX Check List (*To be filled in by applicant or agent*)

A The application contains the following number of sheet(s)

1	Request	1	Sheet(s)
2	Description	35	Sheet(s)
3	Claim(s)	-	Sheet(s)
4	Drawing(s)	-	Sheet(s)
5	Abstract		Sheet(s)

B The application as filed is accompanied by:

1	Priority document	-
2	Translation of priority document	
3	Request for Search	
4	Statement of Inventorship and Right to Grant	

X It is suggested that Figure No ..... of the drawings (if any) should accompany the abstract when published.

XI Signature *(See note 8)*

ELKINGTON AND FIFE (DK/LR)

NOTES:

1. This form, when completed, should be brought or sent to the Patent Office together with the prescribed fee and two copies of the description of the invention, and of any drawings.

2. Enter the name and address of each applicant. Names of individuals should be indicated in full and the surname or family name should be underlined. The names of all partners in a firm must be given in full. Bodies corporate should be designated by their corporate name and the country of incorporation and, where appropriate, the state of incorporation within that country should be entered where provided. Full corporate details, eg "a corporation organised and existing under the laws of the State of Delaware, United States of America," trading styles, eg "trading as xyz company", nationality, and former names, eg "formerly [known as] ABC Ltd." are not required and should not be given. Also enter applicant(s) ADP Code No (if known).

3. Where the applicant or applicants is/are the sole inventor or the joint inventors, the declaration (a) to that effect at IV should be completed, and the alternative statement (b) deleted. If, however, this is not the case the declaration (a) should be struck out and a statement will then be required to be filed upon Patent Form No 7/77.

4. If the applicant has appointed an agent to act on his behalf, the agent's name and the address of his place of business should be indicated in the spaces available at V and VI. Also insert agent's ADP Code No. (if known) in the box provided.

5. An address for service in the United Kingdom to which all documents may be sent must be stated at VI. It is recommended that a telephone number be provided if an agent is not appointed.

6. The declaraton of priority at VII should state the date of the previous filing and the country in which it was made and indicate the file number, if available.

7. When an application is made by virtue of section 8(3), 12(6), 15(4) the appropriate section should be identified at VIII and the number of the earlier application or any patent granted thereon identified.

8. Attention is directed to rules 90 and 106 of the Patent Rules 1982.

9. Attention of applicants is drawn to the desirability of avoiding publication of inventions relating to any article, material or device intended or adapted for use in war (Official Secrets Acts, 1911 and 1920). In addition after an application for a patent has been filed at the Patent Office the comptroller will consider whether publication or communication of the invention should be prohibited or restricted under section 22 of the Act and will inform the applicant if such prohibition is necessary.

10. Applicants resident in the United Kingdom are also reminded that, under the provisions of section 23 applications may not be filed abroad without written permission or unless an application has been filed not less than six weeks previously in the United Kingdom for a patent for the same invention and no direction prohibiting publication or communication has been given or any such direction has been received.

which the phenyl ring is optionally substituted by a halogen atom, a C_{1-4} alkoxy group, a hydroxy group or a C_{1-3} alkyl group;

R_3 represents a hydrogen atom, a C_{1-3} alkyl group or a group $-CO_2R_5$, $-COR_5$, $-COCO_2R_5$ or $-CONHR_5$ where R_5 represents a hydrogen atom, a C_{1-4} alkyl group, a C_{3-7} cycloalkyl group, a C_{2-4} alkenyl group or an aryl or ar(C_{1-4})alkylene group in which the aryl group may be unsubstituted or substituted by a halogen atom, a C_{1-4} alkoxy group, a C_{1-4} alkyl group or a hydroxy group;

R_4 represents a hydrogen atom, a C_{1-3} alkyl group, a C_{3-6} alkenyl group, a phenyl group or a phen(C_{1-3})alkenyl group;

A-B represents the group $CH-CH_2-$ or $C=CH-$;

D represents the group $-CO-$ or $-SO_2-$;

n represents zero or an integer from 1 to 5;

and physiologically acceptable salts solvates (for example hydrates) therof.

All optical isomers of compounds of general formula (I) and their mixtures including the racemic mixtures thereof are embraced by the invention. The invention also includes within its scope all geometric isomers of the compounds of general formula (I).

Referring to the general formula (I), an alkyl group either as such or as part of an alkoxy or phenalkyl group may be a straight chain or branched chain alkyl group such as a methyl, ethyl or prop-2-yl group.

A C_{3-7} cycloalkyl group may be, for example, a cyclopentyl or cyclohexyl group.

A C_{3-6} alkenyl group may be, for example, a propenyl, 2-propenyl or butenyl group. Where R_2 and/or R_4 represents an alkenyl group, it will be appreciated that the double bond may not be adjacent to the nitrogen atom.

When R_2 represents a substituted or unsubstituted phen(C_{1-3})alkyl group, the alkyl moiety of the group is preferably a methyl or ethyl moiety.

A halogen substituent in the compounds of general formula (I) may be, for example, a chlorine, bromine or iodine atom. A C_{1-4} alkoxy group may be, for example, a methoxy or ethoxy group.

CHEMICAL COMPOUNDS

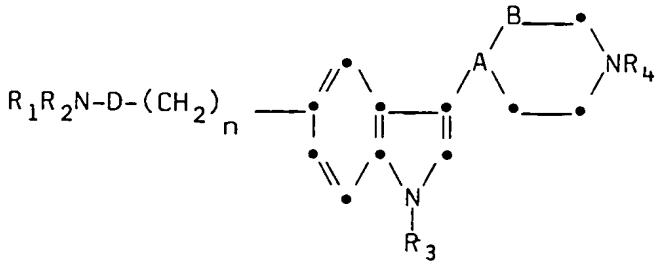
This invention relates to indole derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their medical use, in particular to compounds and compositions of use in the treatment of migraine.

The pain of migraine is associated with excessive dilation of the cranial vasculature and known treatments for migraine include the administration of compounds having vasoconstrictor properties such as ergotamine. However, ergotamine is a non-selective vasoconstrictor which constricts blood vessels throughout the body and has undesirable and potentially dangerous side effects. Migraine may also be treated by administering an analgesic usually in combination with an antiemetic but such treatments are of limited value.

There is thus a need for a safe and effective drug for the treatment of migraine, which can be used either prophylactically or to alleviate an established headache, and a compound having a selective vasoconstrictor activity would fulfil such a role.

We have now found a novel group of indole derivatives having potent and selective vasoconstrictor activity.

Thus, the present invention provides an indole of the general formula (I):



(I)

wherein

R_1 represents a hydrogen atom or a C_{1-6} alkyl group;

R_2 represents a hydrogen atom, a C_{1-6} alkyl group, a C_{3-7} cycloalkyl group, a C_{3-6} alkenyl group, or a phenyl or phen(C_{1-3})alkyl group in

An aryl group, either as such or as part of an ar(C_{1-4})alkylene group is preferably phenyl.

Suitable physiologically acceptable salts of the indoles of general formula (I) include acid addition salts formed with organic or inorganic acids, for example, hydrochlorides, hydrobromides, sulphates, fumarates and maleates. Other salts may be useful in the preparation of compounds of formula (I), e.g. creatinine sulphate adducts.

A preferred class of compounds represented by the general formula (I) is that wherein R_1 represents a hydrogen atom or a C_{1-3} alkyl group such as a methyl group.

Another preferred class of compounds is that wherein R_2 represents a hydrogen atom, a C_{1-3} alkyl group such as methyl or prop-2-yl, or a phenethyl group.

The substituent R_3 in compounds of general formula (I) may be, for example a methyl group but is preferably a hydrogen atom.

A further preferred class of compounds is that in which R_4 represents a hydrogen atom, a C_{1-3} alkyl group such as methyl, or a benzyl group.

n preferably represents zero or an integer 1 to 2

Compounds of the invention selectively constrict the carotid arterial bed of the anaesthetised dog, whilst having a negligible effect on blood pressure. Their selective vasoconstrictor action has also been demonstrated in vitro. They are rapidly absorbed from the gastro-intestinal tract and are suitable for oral administration.

Compounds of the invention are useful in treating pain originating from dilation of the carotid vascular bed, in particular migraine and cluster headache.

Accordingly, the invention also provides a pharmaceutical composition adapted for use in human medicine which comprises at least one compound of formula (I) or a physiologically acceptable salt or solvate (e.g. hydrate) thereof and formulated for administration by any convenient route. Such compositions may be formulated in conventional manner using one or more pharmaceutically acceptable carriers or excipients.

Thus the compounds according to the invention may be formulated for oral, buccal, parenteral or rectal administration or in a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters or ethyl alcohol); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid).

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

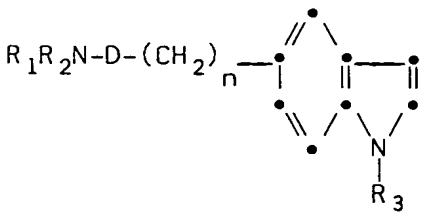
The compounds of the invention may be formulated for parenteral administration by injection. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative.

The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g.

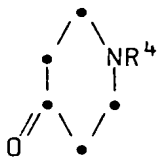
According to another aspect of the invention, compounds of general formula (I) and physiologically acceptable salts and solvates (e.g. hydrates) thereof, may be prepared by the general methods outlined below. In the following processes, R_1, R_2, R_3 and R_4, the group A-B, the group D, and n are as defined for the general formula (I) unless otherwise specified.

According to one general process (A), compounds of formula (I) wherein A-B is the group C=CH may be prepared by condensing a compound of formula (II):



(II)

or a protected or activated derivative thereof, with a piperidone of formula (III):



(III)

or a salt or protected derivative thereof.

The condensation reaction may be effected in a suitable reaction medium in the presence of an acid or a base, conveniently at a temperature of 25 to 120 ^{0}C.

Acids which may be employed in the above process include organic and inorganic acids such as sulphonic acids (e.g. p-toluenesulphonic acid), carboxylic acids (e.g. acetic acid) and preferably strong inorganic acids such as polyphosphoric acid, sulphuric acid and hydrochloric acid. Suitable solvents for the reaction include inert solvents such as ethers (e.g. tetrahydrofuran or dioxan), alcohols (e.g. ethanol) and chlorinated hydrocarbons (e.g. chloroform or carbon

containing conventional suppository bases such as cocoa butter or other glyceride.

For administration by inhalation the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurised packs or a nebuliser, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

A proposed dose of the compounds of the invention for oral, parenteral, buccal or rectal administration to man (of approximately 70kg bodyweight) for the treatment of migraine is 0.1 to 100mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day. It will be appreciated that it may be necessary to make routine variations to the dosage depending on the age and weight of the patient as well as the severity of the condition to be treated.

For oral administration a unit dose will preferably contain from 2 to 50 mg of the active ingredient. A unit dose for parenteral administration will preferably contain 0.2 to 5 mg of the active ingredient.

Aerosol formulations are preferably arranged so that each metered dose or 'puff' delivered from a pressurised aerosol contains 0.2 mg to 2 mg of a compound of the invention, and capsules and cartridges delivered from an insufflator or an inhaler, contain 0.2 mg to 20 mg of a compound of the invention. The overall daily dose by inhalation with an aerosol will be within the range 1 mg to 100 mg. Administration may be several times daily, for example from 2 to 8 times, giving for example 1, 2 or 3 doses each time.

The compounds of the invention may, if desired, be administered in combination with one or more other therapeutic agents, such as analgesics, anti-inflammatory agents and anti-nauseants.

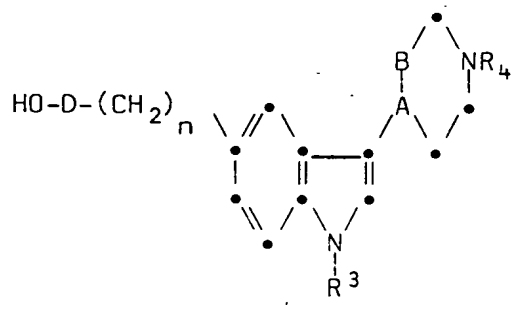
tetrachloride). In some cases the acid may also act as the reaction solvent.

It will be appreciated that in order for the above process to be effected in the presence of a base, R^3 should represent a hydrogen atom.

Bases which may be employed in the above process include alkali metal hydroxides (e.g. potassium hydroxide), alkali metal alkoxides (e.g. sodium or potassium methoxide, ethoxide or t- butoxide), alkali metal hydrides (e.g. sodium hydride) and alkali metal amides (e.g. sodamide). Suitable solvents for the reaction include alcohols (e.g. methanol or ethanol), ethers (e.g. tetrahydrofuran or dioxan) and dimethylsulphoxide.

Intermediates of formula (II) may be prepared by conventional methods for example by reacting an amine of formula R_1R_2NH with the 3-unsubstituted analogues of compounds of formula (IV) (as described hereinafter) using the methods described for process (B) hereinafter.

According to another general process (B), a compound of formula (I) may also be prepared by condensing an amine of formula R_1R_2NH with an acid of general formula (IV)



(IV)

or an acylating agent corresponding thereto, or a salt (for example, an organic or inorganic acid addition salt such as the hydrochloride, hydrobromide, maleate, sulphate or creatinine sulphate adduct) or a protected derivative thereof.

Acylating agents corresponding to the acid of general formula (IV) which may conveniently be used in the above process include acid halides (for example carboxylic acid chlorides and sulphonyl chlorides), alkyl esters (for example the methyl or ethyl esters). activated esters (for example, the 2-(1-methylpyridinyl)ester), mixed

anhydrides (for example, diphenylcarbamic anhydride or pivalic anhydride), or other activated carboxylic acid derivatives such as those conveniently used in peptide synthesis.

The condensation process involving the acylating agents may be effected in a suitable reaction medium which may be aqueous or non-aqueous and conveniently at a temperature of from -70 to +150 °C. Thus the condensation reaction using an acid halide, anhydride or activated ester may be effected in a suitable reaction medium such as an amide (e.g. N,N'-dimethylformamide), an ether (e.g. tetrahydrofuran), a nitrile (e.g. acetonitrile), a haloalkane (e.g. dichloromethane) or mixtures thereof, optionally in the presence of a base such as pyridine or triethylamine or an inorganic base as calcium carbonate or sodium bicarbonate. The condensation reaction using an alkyl ester may be effected in a suitable reaction medium such as an alcohol (e.g. methanol), an amide (e.g. dimethylformamide), an ether (e.g. tetrahydrofuran) or mixtures thereof and conveniently at a temperature of from 0 to 100 °C. In some instances, the amine R_1R_2NH may itself act as reaction solvent.

The reaction involving condensation of an amine R_1R_2NH with a carboxylic acid of general formula (IV) is desirably conducted in the presence of a coupling agent such as carbonyl dimidazole or N,N'-dicyclohexylcarbodiimide. The condensation reaction may be carried out in a suitable reaction medium such as an ether (for example, tetrahydrofuran), a haloalkane (for example, dichloromethane), a nitrile (for example, acetonitrile) or an amide (for example, dimethylformamide) conveniently at a temperature of from -5 to +30 °C. The reaction may also be carried out in the absence of a compling agent in a suitable reaction medium such as a hydrocarbon (for example, toluene or xylene) conveniently at a temperature of from 50 to 120 °C.

Where it is desired to prepare a compound of formula (I) in which R_1 and R_2 are both hydrogen atoms, ammonia may be used in the form of aqueous ammonia or in a solvent such as methanol.

Compounds of formula (IV) and acylating agents corresponding thereto, such as the alkyl esters, are novel and as such constitute a further feature of the invention. Compounds of formula (IV) or acylating agents corresponding thereto may be prepared by methods

techniques. It will be understood that the term 'alkylation' embraces the introduction of an alkyl, cycloalkyl alkenyl or phenylalkyl group. The reaction may be effected using a suitable alkylating agent such as an alkyl halide, alkyl tosylate or dialkylsulphate. The alkylation reaction may conveniently be carried out in an inert organic solvent such as an amide (e.g dimethylformamide) or an ether (e.g. tetrahydrofuran) preferably in the presence of a base. Suitable bases include, for example, alkali metal hydrides, such as sodium hydride, alkali metal carbonates, such as sodium carbonate or alkali metal alkoxides such as sodium or potassium methoxide, ethoxide or t-butoxide. The alkylation reaction is conveniently carried out at a temperature of from 25 to 100 ^{0}C.

According to a still further embodiment, a compound of general formula (I) in which R_3 represents a group $-CO_2R_5$, $-COR_5$, $-COCOR_5$ or $-CONHR_5$ may be prepared by acylating the corresponding compound of formula (I) wherein R_3 represents a hydrogen atom, or a protected derivative thereof. Acylating agents corresponding to the group R^3 which may be used in this general process include acid halides (e.g. acid chlorides such as acetyl chloride); alkyl haloformates (e.g. methyl or ethyl chloro- formate); mixed or symmetrical anhydrides (e.g. acetic anhydride or benzoic anhydride); carbonates (e.g. diethyl carbonate); and isocyanates (e.g. methyl isocyanate).

The reaction is conveniently effected in the presence of a base, such as an alkali metal hydride, e.g. sodium or potassium hydride; an alkali metal carbonate e.g. sodium or potassium carbonate; an alkali metal alkoxide e.g. potassium t-butoxide; butyllithium; or an organic tertiary amine, e.g. triethylamine, or pyridine. Suitable solvents which may be employed in the acylation process include amides e.g. dimethylformamide, or dimethylacetamide; ethers, e.g. tetrahydrofuran or dioxan; halogenated hydrocarbons e.g. methylene chloride; nitriles e.g. acetonitrile and esters e.g. ethyl acetate. The reaction may conveniently be effected at a temperature in the range -10 to +150 ^{0}C.

Alternatively the acylation may be effected in a two-phase reaction medium, in the presence of a phase transfer catalyst, such as tetrabutylammonium hydrogen sulphate or tetraethylammonium bromide. Thus for example the acylating agent may be reacted with a compound of

analogous to those described in UK Patent Specification 2035310 and 'A Chemistry of Heterocyclic compounds - Indoles Part II', Chapter VI, edited by W. J. Houlihan (1972) Wiley Interscience, New York or by processes, such as process (A), as described herein.

According to another general process (C) a compound of formula (I) according to the invention may be converted into another compound of the invention using conventional procedures.

For example, compounds of formula (I) wherein A-B is the group $-CH-CH_2-$ may be prepared by reduction of the corresponding compounds of formula (I) wherein A-B is the group -C=CH-. The reduction process may conveniently be carried out in the presence of hydrogen and a noble metal catalyst, such as palladium, Raney nickel, platinum, platinum oxide or rhodium which may be supported, for example, on charcoal. Alternatively a homogenous catalyst such as tris(triphenylphosphine) rhodium chloride may be used. The reduction may be carried out in a solvent such as an alcohol e.g. methanol or ethanol, an ether e.g. dioxan, an ester e.g. ethyl acetate or an amide e.g. dimethylformamide and conveniently at a temperature of from -10 to $+50\,^{0}C$.

It should be noted however, that the conditions for the reduction of the group A-B when it represents -C=CH-, to the group $-CH-CH_2$, may also effect cleavage of any benzyl groups present or reduction of any other alkenyl group present to an alkyl group.

According to one embodiment of this process, a compound of general formula (I) where A-B represents $-CHCH_2-$ and R_4 is a hydrogen atom, may be prepared by reduction of a corresponding compound of general formula (I) wherein R_4 is a benzyl group, for example with hydrogen in the presence of a catalyst e.g. 10% palladium on charcoal.

According to a further embodiment, a compound of general formula (I) where A-B represents $-CHCH_2-$ and R_2 represents a C_{3-6} alkyl group may be prepared by reduction of the corresponding compound of formula (I) wherein A-B represents C=CH or $-CHCH_2-$ and R_2 represents a C_{3-6} alkenyl group. The reduction process may be effected using the conditions as described above for the reduction of the group A-B.

According to another embodiment of general process (C), a compound of general formula (I) wherein one or more of R_1, R_2, R_3 and R_4represent hydrogen atoms may be alkylated using conventional

be removed by hydrolysis with, for example, hydrogen bromide in acetic acid or by reduction, for example by catalytic hydrogenation. The phthaloyl group may be removed by hydrazinolysis (for example, by treatment with hydrazine hydrate) or by treatment with a primary amine such as methylamine.

As will be appreciated, in some of the general processes (A) to (C) described above it may be necessary or desired to protect any sensitive groups in the molecule as just described. Thus, a reaction step involving deprotection of a protected derivative of general formula (I) or a salt thereof may be carried out subsequent to any of the above described processes (A) to (C).

Thus, according to a further aspect of the invention, the following reactions may, if necessary and/or desired be carried out in any appropriate sequence subsequent to any of the processes (A) to (C).

(i) removal of any protecting groups; and

(ii) conversion of a compound of general formula (I) or a salt thereof into a physiologically acceptable salt or solvate (for example, hydrate) thereof.

Where it is desired to isolate a compound of the invention as a salt, for example as an acid addition salt, this may be achieved by treating the free base of general formula (I) with an appropriate acid, preferably with an equivalent amount, or with creatinine sulphate in a suitable solvent (e.g. aqueous ethanol).

As well as being employed as the last main step in the preparative sequence, the general methods indicated above for the preparation of the compounds of the invention may also be used for the introduction of the desired groups at an intermediate stage in the preparation of the required compound. It should therefore be appreciated that in such multi-stage processes, the sequence of reactions should be chosen in order that the reaction conditions do not affect groups present in the molecule which are desired in the final product.

The invention is further illustrated by the following Examples. All temperatures are in ^{0}C.

formula (I) in an inert organic solvent, (e.g. a halogenated hydrocarbon such as methylene chloride), and an aqueous solution of a base (e.g. 50% sodium hydroxide) containing a phase transfer catalyst.

It will be appreciated that in compounds of general formula (I) wherein R_4 represents hydrogen it will be necessary to protect the group NR_4 during the acylation process. Suitable protecting groups which may be used include conventional amino protecting groups as described for general process (D) hereinafter.

According to another general process (D), a compound of general formula (I) according to the invention, or a salt thereof may be prepared by subjecting a protected derivative of general formula (I) or a salt thereof to reaction to remove the protecting group or groups.

Thus, at an earlier stage in the preparation of a compound of general formula (I) or a salt thereof it may have been necessary and/or desirable to protect one or more sensitive groups in the molecule to prevent undesirable side reactions.

The protecting groups used in the preparation of compounds of formula (I) may be used in conventional manner. See for example 'Protective Groups in Organic Chemistry' Ed.J.F.W. McOmie (Plenum Press 1973) or 'Protective Groups in Organic Synthesis' by Theodora W Greene (John Wiley and Sons 1981).

In compounds of general formula (I) wherein R_4 represents hydrogen the group NR_4 may be protected for example by protonation or with a conventional amino protecting group. Such groups may include for example aralkyl groups, such as benzyl, diphenylmethyl or triphenylmethyl groups; and acyl groups such as N-benzyloxycarbonyl or t-butoxycarbonyl or phthaloyl. The indole nitrogen may also be protected, for example by an aralkyl group such as benzyl. Thus, compounds of general formula (I) wherein one or more of the groups R_3 and R_4 represent hydrogen may be prepared by deprotection of a corresponding protected compound.

Removal of any amino protecting groups present may be achieved by conventional procedures. Thus an aralkyl group such as benzyl, may be cleaved by hydrogenolysis in the presence of a catalyst (e.g. palladium on charcoal); an acyl group such as N-benzyloxycarbonyl may

Example 1

3-[1,2,3,6-Tetrahydro-1-(phenylmethyl)pyridin-4-yl]-1H-indole-5-carboxamide maleate

A suspension of 1H-indole-5-carboxamide (0.4) in glacial acetic acid (20 ml) was heated to 80^0, in a nitrogen atmosphere, and the resulting deep red solution was treated with aqueous phosphoric acid (2N; 7 ml). To the solution was added freshly distilled 1-benzyl-4-piperidone (1.4g) in glacial acetic acid (5 ml) and the reaction mixture was stirred at 70^0 for 18h.

The reaction mixture was cooled, and poured into a mixture of ice and ammonia solution (d 0.88, 50 ml) with ice bath cooling. Ethyl acetate (50ml) was added, the layers were separated and the aqueous layer was extracted with ethyl acetate (4 x 60 ml). The combined organic extracts were dried ($MgSO_4$) evaporated to dryness, and the resulting yellow oil was chromatographed on Merck Kieselgel 60 (100g). Elution with 10% methanol in ethyl acetate and evaporation of the solvent gave a yellow foam which was treated with maleic acid in methanol/ether to give the title compound as yellow microcrystals (0.19g), m.p. $164-166^0$.

Analysis found	C,65.0;H,5.6;N,0.0
$C_{21}H_{21}N_3O.C_4H_4O_4.0.75H_2O$ requires	C,65.2;5.8;N,9.1%

Preparation 1

N-Methyl-1H-indole-5-carboxamide

A mixture of methyl 1H-indole-5-carboxylate (2.5g) and methylamine in water (33%, 50ml) was stirred at room temperature for 6h, all the solid dissolved during this period. The solution was extracted with ethyl acetate (3x50ml) the organic extracts combined, dried (Na_2SO_4) and the solvent removed in vacuo to give a yellow oil. This was chromatographed on silica (Kieselgel 60, 100g) eluting with ethyl acetate to give a colourless oil (1.8g), which solidified on standing m.p. 140-141^{0}C.

T.l.c. Silica, ethyl acetate, Rf 0.38 detection $Ce^{IV}SO_4$, u.v.

Analysis Found: C,69.4;H,5.8;N,16.0.

$C_{10}H_{10}N_2O$ requires C,69.0;H,5.8;N,16.1%.

Example 2

3-[1,2,3,6-Tetrahydro-1-methyl-4-pyridinyl]-1H-indole-5-carboxamide compound with creatinine, sulphuric acid, ethanol and water (2:2:2:1:3)

A solution of 1H-indole-5-carboxamide (0.9g) in glacial acetic acid (30 ml) was heated at 90°C for thirty minutes before phosphoric acid (2N, 10 ml) and N-methyl-4-piperidone (1.4g) were added. After fifteen hours, the solution was cooled, poured into ice-cold ammonia solution (d 0.88) (220 ml) and extracted with ethyl acetate (4 x 80 ml). The combined organic extracts were washed with water (3 x 80 ml), dried and concentrated under vacuum to afford a brown solid (0.72g). Column chromatography (Kieselgel G, 35g) with methanol as eluent afforded the amine (0.47g) as a yellow solid.

The amine (0.25g) was dissolved in a hot mixture of ethanol (12 ml) and water (1.5 ml) before creatinine sulphate (2M, 0.48ml, 0.96mmol) was added. On cooling the title compound crystallised as a pale yellow solid (0.243g) m.p. 228-231°C

Analysis Found: C, 46.4; H, 6.0; N, 16.2;
$C_{15}H_{17}N_3O.C_4H_7N_3O.H_2SO_4.0.5C_2H_5OH.1.5H_2O$ requires: C, 46.5; H, 6.2; N, 16.3%.

Example 3

(i) 3-[1-Methyl-4-piperidinyl]-1H-indole-5-carboxamide

A solution of 3-[1,2,3,6-tetrahydro-1-methyl-4-pyridinyl]-1H-indole-5-carboxamide hydrochloride (1.0g) in ethanol (30 ml) and water (40 ml) was hydrogenated at atmospheric pressure over 10% palladium on charcoal catalyst (0.26g). Hydrogen uptake (83 ml) was complete in 45 min. The resulting suspension was filtered through "hyflo" and the filter cake washed with ethanol-water (1:1, 100 ml). The combined filtrates were evaporated to a gum which was "azeotroped" to dryness with ethanol (2 x 50 ml). The resulting foam was suspended in ether and filtered to give the title compound as a yellow powder, m.p. 118 - 20° dec.(1.09g).

Analysis Found: C, 56.2; H, 7.0; N, 12.7;
$C_{15}H_{19}N_3O.HCl.1.5H_2O.0.25C_2H_5OH$ requires: C, 56.4; H, 7.4; N, 12.7%

The following compounds were similarly prepared:

(ii) N-Methyl-3-(4-piperidinyl)-1H-indole-5-carboxamide 0.2g, m.p. 227-235°, from N-methyl-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1H-indole-5-carboxamide (0.25g) in ethanol and methanol (1:1).

Analysis Found: C,68.4; H,7.5; N,15.2;
$C_{15}H_{19}N_3O.0.25C_4H_8O_2$ requires: C,68.8; H,7.5; N,15.1%

(iii) 3-(4-Piperidinyl)-1H-indole-5-acetamide, maleate 0.16g, m.p. 140-141°, from 3-(1,2,3,6-tetrahydro-4-pyridinyl)-1H-indole-5-acetamide (0.3g) in methanol.

Analysis Found: C,58.7; H,6.4; N,10.6;
$C_{15}H_{19}N_3O.C_4H_4O_4.H_2O$ requires: C,58.3; H,6.4; N, 10.7%

(iv) 3-(1-Methyl-4-piperidinyl)-1H-indole-5-acetamide compound with creatinine, sulphuric acid and water (1:1:1:1) 0.16g, m.p. 174-175° from 3-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-1H-indole-5-acetamide (0.3g) in methanol.

Analysis Found: C,48.1; H,6.6; N, 16.7;
$C_{10}H_{21}N_3O.C_4H_7N_3O.H_2SO_4.H_2O$ requires: C,48.0; H,6.4; N, 16.8%

Example 4

N-Methyl-3-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-1H-indole-5-carboxamide

(i) Methyl 3-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-1H-indole-5-carboxylate

A solution of N-methyl-4-piperidone (0.68g) in phosphoric acid (2N, 4ml) was added to methyl 1H-indole-5-carboxylate (0.5g) in glacial acetic acid at 90° and the mixture was stirred at this temperature for 16h. The mixture was then partitioned between ethyl acetate (100 ml) and water (100 ml). The organic layer was separated and the aqueous layer basified with sodium carbonate and extracted with ethyl acetate (2 x 50 ml). The extracts were washed with water (100 ml) and dried. Removal of the solvent gave a brown solid (0.63g) which was recrystallised from ethyl acetate to give the title compound as yellow microcrystals (0.18g) m.p. 202-204°.

(ii) N-Methyl-3-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-1H-indole-5-carboxamide,

A solution of methyl 3-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-1H-indole-5-carboxylate (0.5g) in a mixture of methylamine in ethanol (40%, 20 ml) and methanol (10 ml) was heated at reflux for 10h. The mixture was cooled, and partitioned between water (100 ml) and ethyl acetate (100 ml). The aqueous phase was separated, and extracted with ethyl acetate (50ml). The organic layers were combined, dried (Na_2SO_4), and evaporated in vacuo to give a pale yellow solid, (0.25g). This was crystallised twice from ethyl acetate to give the title compound as pale yellow microcrystals, (0.1g), m.p. 125-135°C.

Analysis Found: C,69.8; H,7.1; N,15.2;

$C_{16}H_{19}N_3O.0.3H_2O$ requires: C,69.9; H,7.1; N,15.3%

Examole 5

(i) 3-(1,2,3,6-Tetrahydro-4-pyridinyl)-1H-indole-5-carboxamide,

A mixture of 1H-indole-5-carboxamide (1.8g), 4-piperidone hydrochloride monohydrate (3.4g), and potassium hydroxide (11g) in methanol (100 ml) was heated at reflux for 16h. The mixture was cooled, and partitioned between ethyl acetate (200 ml) and saturated potassium carbonate (200 ml). The aqueous phase was separated, and extracted with ethyl acetate (100 ml). The organic extracts were combined, dried (Na_2SO_4), and the solvent evaporated in vacuo to give an orange semi-solid. This was triturated with absolute ethanol (10 ml), and then washed with ether (3x20ml). The resultant pale yellow solid was dried in vacuo to give the title compound, (1.1g), m.p. 225-230°C.

Analysis Found: C,68.2; H,6.3; N,16.3;

$C_{14}H_{15}N_3O.0.2\ C_2H_6O.0.2H_2O$ requires: C,68.0; H,6.5; N,16.5%

The following compounds were similarly prepared:

(ii) N-Methyl-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1H-indole-5-carboxamide . 0.4g, m.p. 233-236° from N-methyl-1H-indole-5-carboxamide (1.3g) and 4-piperidone hydrochloride monohydrate (2.3g).

Analysis Found: C,66.9; H,6.6; N,15.3;

$C_{15}H_{17}N_3O.0.4CH_3OH.0.4H_2O$ requires: C,67.2; H,7.0; N,15.3%

(iii) 3-(1,2,3,6-Tetrahydro-1-methyl-4-pyridinyl)-1H-indole-5-acetamide maleate (0.083g) m.p. 126-127° from indole-5-acetamide (0.16g) and N-methyl-piperidone (0.31 ml) at 55-60°.

Analysis Found: C,59.6; H,6.1; N,10.2;

$C_{16}H_{19}N_3O.C_4H_4O.H_2O$ requires: C,59.5; H,6.3; N,10.4%

(iv) 3-(1,2,3,6-Tetrahydro-4-pyridinyl)-1H-indole-5-acetamide maleate (0.18g) m.p. 180-181° from indole-5-acetamide (0.8g) and 4-piperidone hydrochloride (2.1g) at 60°.

Analysis Found: C,57.8; H,5.7; N,10.2;

$C_{15}H_{17}N_3O_2.C_4H_4O_4.1.5H_2O$ requires: C,57.3; H,6.1; N,10.6%

Example 6

N-Phenylmethyl-3-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-1H-indole-5-carboxamide hydrochloride hemihydrate

(i) N-Phenylmethyl-1H-indole-5-carboxamide

A sample of indole-5-carboxylic acid (3.0g) in anhydrous tetrahydrofuran (THF) (25ml) was treated with 1,1-carbonyldiimidazole (CDI) (3.35g), and stirred at room temperature for 1h. A further amount (1.0g) of CDI was added and, after stirring for a further 1h, benzylamine (4.0g) was introduced. Stirring was continued for 24h. The solution was diluted with water (50ml), saturated with sodium chloride, and the THF layer separated off. After washing the organic solution with 1N hydrochloric acid (3x50ml), brine (2x50ml), and drying ($MgSO_4$) it was evaporated under reduced pressure to afford an oil (6.0g).

This material was chromatographed on silica (Merck 7734, 200g) eluting with methylene chloride and then methylene chloride/methanol (50:1) to give a foam (4.0g). Crystallisation from ethyl acetate/petroleum-ether (b.p. 60-80^0) presented the title compound as a solid (2.05g) m.p. 155-160^0.

Analysis Found: C,76.3;H,5.7;N,10.9.

$C_{16}H_{14}N_2O.0.1C_4H_8O_2$ requires C,76.0;H,5.8;N,10.8%.

(ii) N-phenylmethyl-3-(1,2,3,6-Tetrahydro-1-methyl-4-pyridinyl-1H-indole-5-carboxamide hydrochloride hemihydrate

A solution of the product of stage (i) (1.0g) in 2N methanolic potassium hydroxide (64ml) was treated with distilled N-methyl-4-piperidone (0.47ml) and heated under reflux for 24h with stirring. The mixture was concentrated in vacuo to approximately 10ml and diluted with water (40ml). The crude product separated as a solid (1.1g) which was chromatographed on silica (Merck 7734, (100g) eluting with methylene chloride/ethanol/0.880 ammonium hydroxide (500:8:1) - (25:8:1) to give a solid (0.3g). This material was suspended in methanol (25ml) and treated with excess ethereal hydrogen chloride. The solution was filtered, evaporated to dryness and the residue triturated with anhydrous ether to present the title compound as a powder, (0.382g) m.p. 279-282°.

T.l.c. SiO_2, methylene chloride-ethanol-0.88 ammonia (25:8:1) Rf 0.5 u.v./ipa

Analysis Found: C,67.5;H,6.5;N,10.5.

$C_{22}H_{23}N_3O.HCl0.5H_2O$ requires C,67.6;H,6.45;N,10.7%.

Example 7

N-Phenylethyl-3-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-1H-indole-5-carboxamide hydrochloride

(i) N-Phenylethyl-1H-indole-5-carboxamide

A solution of indole-5-carboxylic acid (3.0g) in anhydrous tetrahydrofuran (THF) (25ml) was treated with 1,1-carbonyl diimidazole (3.35g) and stirred at room temperature for 1.25h. 2-Phenylethylamine (2.36ml) was added and stirring continued for 24h. The mixture was evaporated to dryness and the residue dissolved in ethyl acetate (100ml). The organic solution was washed with 2N hydrochloric acid (4x25ml) and then aqueous 8% sodium bicarbonate solution (4x25ml), before drying ($MgSO_4$) and evaporating under reduced pressure to yield a solid (3.75g). This material was triturated with ether to present the title compound as a powder (3.89g) m.p. 140-3^0

(ii)N-phenylethyl-3-(1,2,3,6-Tetrahydro-1-methyl-4-pyridinyl)-1H-indole-5-carboxamide hydrochloride

A stirred solution of the product of stage (i) (1.0g) in 2N methanolic potassium hydroxide (64ml) was treated with distilled N-methyl-4-piperidinone (0.42ml) and heated under reflux for 18h. A further portion of N-methyl-4-piperidone (0.1ml) was added and the solution heated under reflux for another 6h before allowing to stand at room temperature for 2 days.

The solid was filtered off and dried at 85^0 under vacuum for 18h to afford a solid (0.8g) m.p. $230-5^0$.

A sample (0.2g) was dissolved in warm ethanol (15ml) and treated with excess ethereal hydrogen chloride. The solvent was removed under reduced pressure to present the title compound as a foam (0.2g) m.p. $135-145^0$.

T.l.c. SiO_2, methylene chloride-ethanol-0.88 ammonia (50:8:1) Rf 0.45, u.v./IPA

Water Assay Found: 3.17%

Theory: 3.6%.

Analysis Found: C,66.9;H,6.45;N,9.7.

$C_{23}H_{25}N_3O.HCl.0.82H_2O$ requires C,67.3;H,6.8;N,10.2%.

Example 8

N-(2-Phenylethyl)-3-(1-methyl-4-piperidinyl)-1H-indole-5-carboxamide hydrochloride

A suspension of 10% palladium oxide on carbon (0.55g, 50% paste with water) in ethanol (25ml) was stirred under an atmosphere of hydrogen for 0.5h.

A solution of the product of Example 7 (stage ii) (0.546g) in ethanol/methanol (1:1, 30ml) was added to the pre-reduced catalyst, and the mixture hydrogenated at room temperature and pressure for 3h. The catalyst was filtered off and the solvent removed by rotary evaporation under reduced pressure to leave a foam (0.6g). Chromatography, on silica gel (Merck 7734 50g) eluted with methylene chloride-ethanol-ammonia mixtures, yielded the pure free base as an oil (0.56g). This was dissolved in ethanol/ethyl acetate (1:1, 50ml) and treated with excess ethereal hydrogen chloride. Removal of the solvent by rotary evaporation under reduced pressure gave the title compound as a foam (0.39g) m.p. 110-115^0

T.l.c. SiO_2, methylene chloride-ethanol-0.88 ammonia (25:8:1) Rf 0.75 u.v./IPA.

Analysis Found: C,67.1;H,7.2;N,9.8.

$C_{23}H_{27}N_3O.HCl.0.75H_2O$ requires C,67.1;H,7.2;N,10.2%.

Example 9

N-(1-Methylethyl)-3-(1,2,3,6-tetrahydro-1-methyl-4-pyridyl)-1H-indole-5- carboxamide maleate

(i) N-(1-Methylethyl)-1H-indole-5-carboxamide

A solution of indole-5-carboxylic acid (3.0g) in anhydrous tetrahydrofuran (THF) (25ml) was treated with 1,1-carbonyl diimidazole (3.35g) and stirred at room temperature for 1.5h. Iso-Propylamine (1.6ml) was added and the resulting solution stirred at room temperature for 18h. Removal of the solvent, by rotary evaporation under reduced pressure, produced a foam. This material was dissolved in ethyl acetate (100ml), washed with 2N hydrochloric acid (50ml), then water (2x50ml) before drying ($MgSO_4$) and evaporating to dryness to yield a semi-solid (3.0g).

Chromatography, on silica (Merck 7734 100g) eluting with methylene chloride-methanol (20:1), presented the title compound as a foam (2.2g)

T.l.c. SiO_2, methylene chloride-methanol (20:1) Rf 0.5 u.v.

Analysis Found: C,71.3;H,7.0;N,13.85.

$C_{12}H_{14}N_2O$ requires C,70.9;H,7.0;N,13.6%.

(ii)N-(1-Methylethyl)-3-(1,2,3,6-Tetrahydro-1-methyl-4-pyridyl)-1H-indole-5-carboxamide maleate

A solution of the product of stage (i) (1.0g) and distilled N-methyl-4-piperidone (0.56ml) in 2N methanolic potassium hydroxide (64ml) was stirred under reflux for 24h. During this period a solid separated. The cooled suspension, was filtered and the solid collected and dried (0.85g). A sample of this material (0.6g) was chromatographed on silica (Merck 7734: 32g) eluted with methylene chloride-ethanol-0.88 ammonia mixtures, to yield the pure free base as a pale yellow powder (0.5g) m.p. 240-5^0.

A hot solution of the base (0.34g) in methanol (20ml) was treated with a hot solution of maleic acid (0.1326g) in ethyl acetate (10ml). The boiling solution was concentrated to half volume and then diluted with an equal volume of hot ethyl acetate. This procedure was repeated and the solution allowed to cool whereupon the product crystallised. The solid was collected by filtration, washed with ethyl acetate (10ml) and dried to present the maleate salt as a powder (0.43g) m.p. 175-80^0

T.l.c. SiO_2, methylene chloride-ethanol-ammonia (50:8:1)) Rf 0.4 u.v./IPA.

Water Analysis Found: 2.01%.

Theory 2.13%.

Analysis Found: C,62.4;H,6.3;N,9.8.

$C_{18}H_{23}N_3O.C_4H_4O_4.0.5H_2O$ requires C,62.55;H,6.7;N,9.95%.

with anhydrous ether to give the title compound free base as a powder (0.122g) m.p. 217-223°

A solution of the free base (0.1g) in hot methanol (3mℓ)/ethyl acetate (2mℓ) was treated with a hot solution of oxalic acid (0.033g) in absolute alcohol (0.5mℓ). The resultant solution was concentrated to low volume whereupon the product crystallized. This material was filtered off and washed with analar ethyl acetate (2mℓ) to give the title compound as a powder (0.104g) m.p. 145-150°.

Water Assay Found: 0.6% Theory 0.6%.

Analysis Found: C,58.8;H,5.95;N,10.9.

$C_{16}H_{19}N_3O.C_2H_2O_4.0.27CH_4O.0.12C_2H_6O.$
$0.12C_4H_8O_2O.13H_2O$ requires C,59.0;H,6.3;N,10.9%.

Example 12

N,N-Dimethyl-3-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-1H-indole-5 carboxamide oxalate

(i) N,N-Dimethyl-1H-indole-5-carboxamide

A solution of indole-5-carboxylic acid in anhydrous tetrahydrofuran (THF) (25ml) was treated with 1,1'carbonyldiimidazole (CDI) (3.35g) and stirred at room temperature for 1.5h. A further portion of C.D.I. (0.7g, 0.0043mol) was added and stirring continued for 18h.

The solution was cooled to about 2° (ice-bath) and dimethylamine gas bubbled through the solution for 10min. The solution was stirred at room temperature for 6h and then dimethylamine gas bubbled through for a further 10min before stirring at room temperature overnight. The suspension was filtered and the white solid collected and washed with dry THF (10ml), to give a solid (~ 2.9g) m.p. 235-238°, which was crystallised from methanol to give the title compound as microcrystals (1.128g) m.p. 235-8°

(ii) N,N-Dimethyl-3-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-1H-indole-5-carboxamide oxalate

A suspension of the product of stage (i) (0.7g) in 2N methanolic - potassium hydroxide (2mℓ) containing distilled N-methyl-4-piperidone (0.48mℓ) was stirred with heating at reflux for 2h. The suspension

Example 10

N-(1-Methylethyl)-3-(1-Methyl-4-piperidinyl)-1H-indole-5-carboxamide hydrochloride

A suspension of 10% palladium oxide on carbon (0.85g of a 50% paste in water) in ethanol (50ml) was stirred under hydrogen for 0.5h. A solution of product of Example 9 as the free base (0.85g) in a mixture of 1:1 ethanol-methanol (200ml) was added to the pre-reduced catalyst and the mixture stirred under an atmosphere of hydrogen for 4h. The catalyst and solvent were removed, by filtration and rotary evaporation respectively to give a foam (0.8g) which was chromatographed on a column of silica gel (40g of Merck 7734) eluted with methylene chloride/ethanol/0.88 ammonia (50/8/1) to give the title compound free base as a foam (0.7g).

The free base (0.7g) was dissolved in ethanol (10ml) and treated with excess ethereal hydrogen chloride. Removal of the solvent, by rotary evaporation, and drying under vacuum at 60^0 for 18 h gave the title compound as a foam (0.63g) m.p. 190-200^0.

Analysis Found : C,61.0; H,7.8; H,11.3

$C_{18}H_{25}N_{30}.HCl.H_2O$ requires C,61.1; H,7.8; N,11.9%

Example 11

1-Methyl-3-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-1-methyl-1H-indole-5-carboxamide oxalate

N-methyl-4-piperidone (0.37mℓ) and 2N phosphoric acid (1mℓ) was added to a stirred solution of 1-methyl indole-5-carboxamide (0.2g) in glacial acetic acid (5mℓ) under a nitrogen atmosphere and heated to 100^0 (oil bath temp) for 24h. The solution was poured onto a mixture of saturated potassium carbonate solution (20mℓ) and water (10mℓ) and the resultant solid was filtered off and washed with ethanol (3x20mℓ). Extraction of the potassium carbonate solution with ethyl acetate (30mℓ) and ethanol (3x30mℓ), followed by evaporation of the combined extracts and ethanol washing gave a solid (4.0g) which was chromatographed on a column of silica gel (20g of Merck 7734) eluted with dichloromethane/ethanol/0.88 ammonia (100/8/1). Evaporation of the appropriate fractions gave a residue (0.16g) which was titrated

was filtered and the solid washed with dry ether to give the crude product as a solid (0.75g). This material was chromatographed on a column of silica gel (50g of Merck 7734) eluted with methylene chloride/ethanol/ammonia (100/8/1). Evaporation of the appropriate fractions gave a solid (about 0.13g) which was triturated with anhydrous ether and filtered to give the pure title compound free base as a powder (0.11g) m.p. 203-205°.

A solution of the free base (0.08g) in hot absolute alcohol (4mℓ) was treated with a hot solution of oxalic acid (0.025g) in absolute alcohol (0.5mℓ) and the solution was evaporated to approximately half volume whereupon the salt began to crystallise out. Absolute alcohol (3mℓ) was added and the solid was filtered off and washed with ethyl acetate (~2mℓ) to give the title compound as a powder (0.058g) m.p. 141-146°

T.l.c. [SiO_2, ethanol/methylene chloride/ammonia (100/8/1) Rf 0.3 uv/IPA.

Analysis Found: C,59.2;H,5.9;N,10.9.

$C_{17}H_{21}N_3O.C_2H_2O_4.0.6H_2O$ requires C,59.4;H,6.3;N,10.9%.

Example 13

1-Methyl-3-(1-methyl-4-piperidinyl)-1H-indole-5-carboxamide oxalate

A suspension of the free base of the product of Example 11 (0.69g) in ethanol (100mℓ)/dimethylformamide (1mℓ) was added to a slurry of pre-reduced 10% palladium oxide on carbon (0.8g of a 50% paste in water) in ethanol (50mℓ). The resulting suspension was stirred rapidly under an atmosphere of hydrogen at room temperature and atmospheric pressure until uptake of hydrogen had ceased. The catalyst and solvent were removed by filtration and rotary evaporation respectively, to give a gum (about 1.0g) which was chromatographed on a column of silica gel (50g of Merck 7734) eluted with methylene chloride/ethanol/0.88 ammonia (100/8/1). Evaporation of the appropriate fractions gave the pure title compound free base as an oil (0.68g), a sample of which (0.63g) in hot absolute alcohol (10mℓ) was treated with a hot solution of oxalic acid (0.21g) in absolute alcohol (2mℓ). Upon cooling the solution was scratched to give the title compound as a powder (0.53g) m.p. 200-5°

Analysis Found C,59.3;H,6.4;N,11.3.
$C_{16}H_{21}N_3O.C_2H_2O_4.0.1H_2O$ requires C,59.5;H,6.4;N,11.6%.

Example 14

N,N-Dimethyl-3-(1-methyl-4-piperidinyl)-1H-indole-5-carboxamide oxalate

A suspension of 10% palladium oxide on carbon (0.6g of a 50% paste with water) in ethanol (50mℓ) was stirred under hydrogen for 0.5h. The product of Example 12 as the free base (0.55g) in ethanol (50mℓ) was added and hydrogenated at room temperature and atmospheric pressure until uptake of hydrogen had ceased. The catalyst and solvent were filtered off and evaporated respectively to leave a foam (0.49g) which was chromatographed on silica gel (35g of Merck 7734) eluted with methylene chloride/ethanol 0.88 ammonia (100/8/1). Evaporation of the appropriate fractions gave the pure title compound free base as a powder (0.3g) m.p. 175-177°, a sample of which (0.27g) in hot analar ethyl acetate was treated with methanol (1mℓ) and a solution of oxalic acid (0.86g) in absolute ethanol (1mℓ). The solution was concentrated to approximately half volume, cooled and scratched causing a thick cream solid to crystallise. This was treated with absolute alcohol (3mℓ), filtered and the washed with absolute alcohol (2mℓ) to give the title compound as a powder (0.24g) m.p. 120-5° (dec)

Analysis Found: C,58.8;H,6.8;N10.1
$C_{17}H_{23}N_3O.C_2H_2O_4.0.33C_2H_6O.0.17C_4H_8O_2.0.4H_2O$
requires C,59.2;H,7.1;N,10.2%

Example 15

3-(1,2,3,6-Tetrahydro-1-methyl-4-pyridinyl)-1H-indole-5-sulphonamide

A solution of 1H-indole-5-sulphonamide (0.4g) in methanolic potassium hydroxide (2N, 30mℓ) containing 1-methyl-4-piperidone (0.24ml) was heated at reflux for 7h. Further 1-methyl-4-piperidone (0.24mℓ) was added after 2h. The cooled reaction mixture was neutralised to pH 7 with glacial acetic acid and evaporated to dryness. The residue was partitioned between sodium bicarbonate solution (8%, 100mℓ) and ethyl acetate (4x100mℓ). The combined organic extracts were washed with

water (50mℓ), dried (Na_2SO_4) and evaporated to dryness to give a foam (0.7g) which was purified on a silica column (Kieselgel 60, 50g) eluted with ethyl acetate/methanol/ammonia (180:20:1). Evaporation of the appropriate fractions to small volume followed by cooling and scratching gave the title compound as a crystalline solid (0.3g) m.p. 190-200°.

Analysis Found: C,57.1; H,6.3; N,12.4.
$C_{14}H_{17}N_3O_2S.0.5C_4H_8O_2$ requires C,57.3; H,6.3; N,12.5%.

Example 16

N,N-Dimethyl-3-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-1H-indole-5-sulphonamide hemihydrate

A solution of N,N-dimethyl-1H-indole-5-sulphonamide (1.1g) in methanolic potassium hydroxide (2N, 30mℓ) containing N-methyl-4-piperidone (0.85g) was heated at reflux for 16h. The cooled mixture was diluted with ethyl acetate (200mℓ) and washed with brine (4x50mℓ) dried (Na_2SO_4) and evaporated to small volume to deposit the title compound as a crystalline solid (0.9g).
This material was purified on a flash column of silica (4cm diameter) eluted with the above solvent. Evaporation of the appropriate fractions to small volume deposited the title compound as a pale solid (0.2g) m.p. 230-232° (dec).

Analysis Found: C,58.8; H,6.4; N,12.5.
$C_{16}H_{21}N_3O_2S.0.5H_2O$ requires C,58.5; H,6.75; N,12.8%.

Example 17

N-Methyl-3-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-1H-indole-5-methanesulphonamide hydrochloride

A solution of N-methylo-1H-indole-5-methanesulphonamide (0.43g) in methanol (5mℓ) containing potassium hydroxide (0.43g) and N-methyl-4-piperidone (0.47mℓ) was stirred under reflux for 6h. The solution was dried with anhydrous magnesium sulphate (3.0g), evaporated to dryness and purified by flash chromatography eluted with dichloromethane/ethanol/0.88 ammonia (100/8/1). Evaporation of the appropriate fractions gave a solid (0.39g) which was purified by

further flash chromatography to give the free base of the title compound as a foam (0.27g) m.p. 185-190°.

A solution of the free base (0.1g) in a mixture of absolute alcohol (2mℓ) and ethyl acetate (2mℓ) was treated with excess ethereal hydrogen chloride. The resulting solution was evaporated to dryness and the residue stirred with ethyl acetate to give the title compound as a solid (0.77g) m.p. 120 (decomp)

Analysis Found: C,51.5; H,6.6; N,10.6.

$C_{16}H_{21}N_3O_2S.HCl.0.85H_2O.0.2C_4H_8O_2$ requires C,51.9; H,6.6; N,10.8%.

Example 18

N-Methyl-3-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-1H-indole-5-ethane sulphonamide oxalate

A solution of N-methyl-1H-indole-5-ethanesulphonamide (1.0g) in methanol (50mℓ) containing potassium hydroxide (5.6g) and N-methyl-4-piperidone (1.0mℓ) was heated at reflux for 24h, cooled, and the resulting solid filtered off (1.0g). A sample of the solid (0.2g) was dissolved in a hot methanolic solution of oxalic acid (0.06g), the solution cooled, and the salt precipitated by adding ethyl acetate (20mℓ) and dry ether (50mℓ). The salt was filtered off, and dried in vacuo to give the title compound as a solid (0.12g) m.p. 87°-90° (shrinks) Analysis Found: C,52.2;H,5.6;N,9.5.

$C_{17}H_{23}N_3O_2S.C_2H_2O_4.0.6H_2O$ requires C,52.5;H,6.0;N,9.7%.

Example 19

3-(1-Methyl-4-piperidinyl)-1H-indole-5-sulphonamide hydrochloride

A solution of the free base of the product of Example 15 (0.7g) in methanol (70mℓ) was hydrogenated over palladium oxide on charcoal (10%, 50% aq. paste, 0.2g) and platinum oxide on charcoal (10%, 0.2g) at room temperature and pressure until hydrogen uptake ceased. The catalyst was filtered off, washed with ethanol and the filtrate evaporated to small volume to deposit the free base of the title compound as a crystaline solid (0.25g). This material was dissolved in methanol (5mℓ) treated with ethereal hydrogen chloride and diluted with dry ether (150mℓ) to give a solid which was crystallised from isopropanol to give the title compound as a crystalline solid (0.1g) m.p. 195-198° (decomposes) (shrinks with bubbling at 148-150°).

Analysis Found: C,51.3; H,7.0; N,10.7.
$C_{14}H_{19}N_3O_2S.HCl.0.5H_2O.C_3H_8O$ requires C,51.2; H,7.3; N,10.5%.

Example 20

3-(1-Methyl-4-piperidinyl)-1H-indole-5-methanesulphonamide hydrochloride

A solution of the free base of the product of Example 17 (0.17g) in a mixture of absolute alcohol (5mℓ)/methanol (5mℓ) was added to a stirred slurry of pre-reduced palladium oxide on carbon (0.2g of a 50% paste in water) in absolute alcohol (10mℓ). The suspension was stirred under hydrogen for 21.5h.

Further catalyst (0.2g) was added and the hydrogenation continued for a further 24h. The catalyst and solvent were removed by filtration and rotary evaporation to give a foam (0.09g) which was purified by chromatography on silica (Merck 7734,10g) eluting with dichloromethane/ethanol/0.88 ammonia (100/8/1) to give the free base of the title compound as a foam (0.07g). A solution of the free base (0.07g) in absolute alcohol (2mℓ) was treated with excess ethereal hydrogen chloride. Removal of the solvent (by rotary evaporation) yielded a foam which was triturated with anhydrous ether to give the title compound as a powder (0.07g) m.p. 140-5° (dec)

Water Assay Found: 2.7
Theory: 2.4%

Analysis Found: C,52.5; H,7.5; N,10.75.
$C_{16}H_{23}N_3O_2S.HCl.0.5H_2O.0.3\ C_2H_6O$ requires C,52.4; H,7.1; N,11.0%.

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